



## General

### Guideline Title

Guideline on the management of bleeding in patients on antithrombotic agents.

### Bibliographic Source(s)

Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol*. 2013 Jan;160(1):35-46. [PubMed](#)

### Guideline Status

This is the current release of the guideline.

## Recommendations

### Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

#### Specific Measures

##### Parenteral Anticoagulants

##### *Unfractionated Heparin (UFH)*

- Stopping an UFH infusion and general haemostatic measures are often sufficient to stop or prevent bleeding (2C).
- Protamine sulphate (1 mg per 80–100 units UFH) will fully reverse UFH, but should be given slower than 5 mg/min to minimize the risk of adverse reactions.
- The maximum recommended dose of 50 mg protamine is sufficient to reverse UHF in most settings.

##### *Low Molecular Weight Heparin (LMWH)*

- LMWH administration within 8 hours of the time of requirement for correction of anticoagulation: give protamine sulphate (1 mg per 100 anti-Xa units of LMWH). If ineffective, consider further protamine sulphate 0.5 mg per 100 anti-Xa units (2C). Protamine sulphate should be given slower than 5 mg/min to minimize the risk of adverse reactions.
- LMWH administration greater than 8 hours from the time of requirement for correction of anticoagulation: consider smaller doses of protamine (2C).
- Consider recombinant activated factor VII (rFVIIa) if there is continued life-threatening bleeding despite protamine sulphate and the time

frame suggests there is residual effect from the LMWH contributing to bleeding. (2C).

#### *Danaparoid Sodium*

- There is no specific antidote for danaparoid. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
- Plasmapheresis may be considered for critical bleeding.

#### *Fondaparinux*

- There is no specific antidote for fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
- Recombinant FVIIa should be considered for critical bleeding (2C).

#### *Bivalirudin*

- There is no specific antidote for bivalirudin. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
- Exceptionally, haemodialysis, haemofiltration or plasmapheresis may be considered for critical bleeding (2C).

#### *Argatroban*

- There is no specific antidote for argatroban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).

#### Oral Anticoagulants

##### *Warfarin*

- All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (PCC) (1C).
- Emergency anticoagulation reversal in major bleeding should be with 25–50 U/kg four-factor PCC and 5 mg intravenous vitamin K (1B).
- Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).
- Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if PCC is not available (1C).
- Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B).
- Patients with an international normalized ratio (INR) >5.0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be reduced (1B). The cause of the elevated INR should be investigated (1C).
- Asymptomatic patients with an INR of  $\geq 8.0$  should receive 1–5 mg of oral vitamin K (1B). The INR should be rechecked the following day in case an additional dose of vitamin K is required.
- For surgery that requires reversal of warfarin and that can be delayed 6–12 hours, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed for vitamin K to have time to take effect, the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).

##### *Other Vitamin K Antagonists*

- Emergency reversal of the effect of phenprocoumon, acenocoumarol and phenindione should be with 5 mg intravenous vitamin K and 25–50 units/kg four-factor PCC.
- For less severe bleeding or for correction of over anticoagulation, 1–5 mg of oral vitamin K is sufficient.

##### *Direct Oral Thrombin Inhibitors – Dabigatran*

- There is no specific antidote for dabigatran. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
- In bleeding patients who have taken a dose of dabigatran in the last 2 hours, consider oral activated charcoal to prevent further absorption (2C).
- If rapidly deployable, haemodialysis, haemofiltration and charcoal haemoperfusion offer the possibility of enhanced clearance of the active drug (2C).
- In situations with ongoing life-threatening bleeding PCC, activated prothrombin complex concentrate (APCC), and rFVIIa should be considered (2C).

##### *Direct Oral Xa Inhibitors – Rivaroxaban and Apixaban*

- There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).
- In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered (2C).

#### Anti-platelet Drugs

- Decisions to withhold anti-platelet drugs or to administer pro-haemostatic agents should be made after a careful multi-disciplinary assessment of the risks and benefits of intervention. (1C).
- Bleeding in patients during treatment with aspirin, P2Y<sub>12</sub> antagonists or glycoprotein (GP) IIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of coprescribed anticoagulants should also be considered (2C).
- Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery (2C).
- Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia ( $<10 \times 10^9/l$ ) caused by abciximab (2C).

#### Fibrinolytic Drugs

For major bleeding (e.g., intracerebral) within 48 hours of administration, the task force recommends:

- Stop infusion of fibrinolytic drugs and other antithrombotic drugs (1C).
- Administer fresh frozen plasma 12 ml/kg (2C).
- Administer intravenous tranexamic acid 1 g tds (2C).
- If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate (2C).
- Further therapy should be guided by results of coagulation tests (2C).

#### Definitions:

##### Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

##### Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

#### Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Bleeding during antithrombotic therapy

## Guideline Category

Management

Treatment

## Clinical Specialty

Anesthesiology

Cardiology

Critical Care

Emergency Medicine

Hematology

Internal Medicine

Pharmacology

Surgery

## Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Hospitals

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To guide healthcare professionals in the United Kingdom on the management of patients receiving antithrombotic drugs who experience significant bleeding or who require emergency surgery or an invasive procedure

## Target Population

All patients receiving antithrombotic agents who are bleeding or are at risk for bleeding

## Interventions and Practices Considered

1. Management of bleeding associated with parenteral anticoagulants
  - Cessation of anticoagulant treatment
  - General haemostatic measures
  - Protamine sulphate (for reversing unfractionated heparin and low molecular weight heparin)
  - Recombinant activated factor VII (rFVIIa)
  - Haemodialysis, haemofiltration, or plasmapheresis for critical bleeding
2. Management of bleeding associated with oral anticoagulants
  - Reversal with four-factor prothrombin complex concentrate (PCC)
  - Oral or intravenous vitamin K
  - Fresh frozen plasma (if PCC is not available)
  - Withholding doses of warfarin in patients with international normalized ratio (INR) >5 but no bleeding
  - Cessation of treatment and general haemostatic measures
  - Oral activated charcoal to prevent further anticoagulant absorption
  - Haemodialysis, haemofiltration, and charcoal haemoperfusion
  - In situations with ongoing life-threatening bleeding: PCC, activated prothrombin complex concentrate (APCC), and rFVIIa
3. Management of bleeding associated with oral antiplatelets
  - Withholding antiplatelet drugs or administering pro-haemostatic agents after a careful multi-disciplinary assessment of the risks and benefits of intervention
  - General haemostatic measures
  - Drug cessation and reversal of the effect of coprescribed anticoagulants
  - Platelet transfusion for critical bleeding, prevention of bleeding before emergency surgery, or prevention of bleeding in severe thrombocytopenia caused by abciximab
4. Management of major bleeding associated with fibrinolytics
  - Stopping infusion of fibrinolytic drugs and other antithrombotic drugs
  - Fresh frozen plasma
  - Intravenous tranexamic acid
  - Cryoprecipitate or fibrinogen concentrate
  - Further therapy guided by results of coagulation tests

## Major Outcomes Considered

- Morbidity
- Mortality
- Reversal of anticoagulant effect
- Bleeding, haemorrhagic, and thrombotic risks
- Stroke

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

The MEDLINE and EMBASE databases were searched systematically for publications in English from 1966 to June 2011 and 1980 to June 2011, respectively, using the following strategy: Approved and proprietary names of the antithrombotic agents described in the guideline were combined with terms relating to antidote, reversal, haemorrhage, (activated) prothrombin complex concentrate, factor VIII inhibitor bypass

activity, Beriplex, Octaplex, recombinant activated factor VII, Novoseven, fresh frozen plasma, tranexamic acid, antifibrinolytic, platelet transfusion, and desmopressin. Identified papers were also searched for additional references.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

### Quality of Evidence

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(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

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(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

## Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of United Kingdom-based medical experts.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology.

# Rating Scheme for the Strength of the Recommendations

## Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom haematologists, the British Committee for Standards in Haematology, and the British Society for Haematology Committee and comments incorporated where appropriate.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate management of bleeding in patients receiving antithrombotic agents

## Potential Harms

- Recombinant activated factor VII is often considered as a last resort when all other measures have failed and the risks and benefits are carefully documented.
- Prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (APCC) agents may increase thrombosis risk although this has not been evaluated in large-scale meta-analyses.
- Protamine can cause severe allergic reactions, including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients. Risk factors are previous exposure to protamine sulphate (including protamine-containing insulin preparations), rate of administration, vasectomy, and fish allergy.
- Many patients who are prescribed anti-platelet drugs are at high risk of arterial thrombosis. Therefore, the safety of anti-thrombotic drug withdrawal and pro-haemostatic interventions should be considered carefully through a multi-disciplinary risk assessment.
- Platelet transfusion may be considered for emergency reversal of the anti-platelet effect but may confer a risk of arterial thrombosis.

# Contraindications

## Contraindications

Desmopressin is relatively contraindicated in patients with cardiovascular disease, and there is no evidence to support efficacy in this patient group.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Staying Healthy

## IOM Domain

Effectiveness

Safety

Timeliness

# Identifying Information and Availability

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## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2013 Jan

## Guideline Developer(s)



## Source(s) of Funding

British Committee for Standards in Haematology

## Guideline Committee

Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Not stated

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: Available from the [British Committee for Standards in Haematology Web site](#) .

Print copies: Available from the British Committee for Standards in Haematology; Email: [bcsh@b-s-h.org.uk](mailto:bcsh@b-s-h.org.uk)

## Availability of Companion Documents

None available

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on January 15, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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